REMARKS

I. Discussion of Possession, Enablement, and Definiteness

The Patent Office rejected the claims under 35 USC 112, first paragraph, and 35 USC 112, second paragraph. The Patent Statute requires, under 35 USC 112, first paragraph, that the specification contain a written description of the invention, and of the manner and process of making and using it, in such terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and, under 35 USC 112, second paragraph, that the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the invention. The Patent Office takes the position that the possession issue is governed by *University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).[1] *Accord*, MPEP § 2163 at page 2100-162, col. 1 ("A definition by function alone 'does not suffice' to sufficiently describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is.").[2] The Patent Office also takes the position that the enablement issue is governed by *Ex parte Balzarini*, 21 USPQ2d 1892, 1894 (BPAI 1991) (Claims directed to medicinal treatments of diseases in highly unpredictable art areas are properly rejected under 35 USC § 112, first paragraph as lacking adequate enablement, in the absence of sufficient test data in support of the efficacy of the alleged treatment).[3] *Accord*, MPEP § 2107.03 at page 2100-44, col. 2.[4] As for the definiteness issue, it is governed by MPEP § 2173.05(r), which states that some applications are filed with an omnibus claim that reads as follows: "A device substantially as shown and described."[5] An omnibus claim should be rejected under 35 USC 112, second paragraph, because it fails to particularly point out and distinctly claim the invention.

As stated by the Patent Office, the enablement issue is governed by *Ex parte Balzarini*, 21 USPQ2d 1892, 1894 (BPAI 1991) (Claims directed to medicinal treatments of diseases in highly unpredictable art areas are properly rejected under 35 USC § 112, first paragraph as lacking adequate enablement, in the absence of sufficient test data in support of the efficacy of the alleged treatment). *Accord*, MPEP § 2107.03 at page 2100-44, col. 2. The present case follows

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[1] Attachment 1 of record.
[2] Attachment 2 of record.
[3] Attachment 3 of record.
[4] Attachment 4 of record.
[5] Attachment 5 of record.

Ex parte Balzarini, because in *Ex parte Balzarini*, the evidence of record is a Declaration by Dr. Hirsch that only concludes that the test methods used in the patent specification "may" establish the compounds have utility in humans, and any conclusion as to whether a specific anti-viral compound "will" in fact be effective *in vivo* is not agreed to be predictive from the *in vitro* tests. The Declaration under 37 CFR 1.132 of Dr. Jorge R. Vila is directed to these issues (of record and having Dr. Vila's Curriculum Vitae attached as Exhibit 1).* It states that the test methods using *quiescent* human peripheral blood lymphocyte (PBL) cells as outlined in Malley et al., Proc. Natl. Acad. Sci. USA 91:11017 (1994)[6] (identifying synergistic effect of hydroxyurea and 2', 3'-dideoxyinosine (ddI)), of which he is the last-named author, are accepted by those skilled in the anti-human immunodeficiency virus (HIV) art as providing a reasonable basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo*, because the combination of hydroxyurea and ddI is effective *in vivo* and predictive from the *in vitro* tests using quiescent human PBL cells, as demonstrated by human clinical trials, per Vila et al., Lancet 350:635 (1997),[7] of which he is the first-named author. Additionally, the Declaration of Dr. Vila states that the test methods using *activated* human PBL cells as outlined in Gao et al., Proc. Natl. Acad. Sci. USA 90:8925 (1993)[8] and Lori et al., Science 266:801 (1994)[9] (identifying synergistic effect of hydroxyurea and ddI) are also accepted by those skilled in the anti-HIV art as providing a reasonable basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo*, because the combination of hydroxyurea and ddI is effective *in vivo* and predictive from the *in vitro* tests using activated human PBL cells, as demonstrated by human clinical trials, per Vila et al., above. The Declaration of Dr. Vila concludes that, although the test methods using quiescent human PBL cells may provide a *better* basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo* (because viral DNA synthesis is known to take place in quiescent cells), the test methods using activated human PBL cells provide a *reasonable* basis for this conclusion

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* See Declaration under 37 CRF 1.132 of Nancy W. Vensko of record explaining that Dr. Vila has a financial interest in the above-identified application.

[6] Attachment 6 of record.

[7] Attachment 7 of record.

[8] Attachment 8 of record.

[9] Attachment 9 of record.

(because a conclusion as to whether the combination would be effective *in vivo* was predictive from the *in vitro* tests), and that a conclusion as to whether a specific anti-viral compound will in fact be effective *in vivo* is reasonably predictive from the *in vitro* tests using activated human PBL cells. As agreed by *Ex parte Balzarini*, claims directed to medicinal treatments of diseases in highly unpredictable art areas meet the requirements of 35 USC § 112, first paragraph for providing amble enablement, in the presence of sufficient test data in support of the efficacy of the alleged treatment, where, as here, the test data is reasonably predictive (even if not perfect, i.e., by virtue of identifying AZT). Under *Ex parte Balzarini*, the claims meet the enablement requirement. The Patent Office maintained its rejection of the claims despite the Declaration of Dr. Vila. The opinion of a qualified expert, however, must be accepted by the PTO. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). The Patent Office's answer that the specification describes only one working example, that of use of a combination of ddI and hydroxyurea, does not refute the thrust of the declaration which is that one with ordinary skill in the art would have understood the specification to enable use of a combination of the class of compounds to which ddI belongs in combination with the class of compounds to which hydroxyurea belongs. The specification teaches a representative combination that works. The claims are enabled because one skilled in the art could make and use other combinations by following the specification for directions on how to do so. One skilled in the art would merely have to substitute a different combination and test it in the *in vitro* PBL model attested by Dr. Vila as being reasonably predictive of *in vivo* results. Any experimentation here would not be considered by those skilled in the art undue, because it is ordinary and requires no ingenuity beyond that to be expected of one of ordinary skill in the art. Because the experimentation would not be undue, the evidence weighs in favor of enablement. Additionally, see Declaration of Dr. Lori,[10] a named inventor of the above-identified application, which provides post-filing date evidence of other representative combinations that work, as predicted by the patent specification, further supporting enablement.

As stated by the Patent Office, the possession issue is governed by *University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). *Accord*, MPEP § 2163 at page 2100-162, col. 1 ("A definition by function alone 'does not suffice' to sufficiently describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is."). MPEP § 2163 at page 2100-164, paragraph bridging col. 1 and col. 2 does not say, however, that

[10] Of record.

the written description requirement for a claimed genus may never be satisfied. Rather, it says that the written description requirement for a claimed genus may indeed be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. The Declaration of Dr. Vila is directed to these issues. It states that, in view of the combination of hydroxyurea, a ribonucleotide reductase inhibitor, and ddI, a nucleoside reverse transcriptase inhibitor (NRTI), it is obvious that this principle should be viable for the combination of other NRTIs, and that any modality that would deplete the intracellular pool of deoxyribonucleotide phosphates could substitute for hydroxyurea. *Accord,* J. Balzarini, Pharmacology & Therapeutics 87: 175-187 (2000) at page 176, col. 2, last line before section 2, and page 179, col. 2, first line of new paragraph.[11] *See also,* Malley et al., Lancet 343:1292 (1994) (substitution of DAH, another ribonucleotide reductase inhibitor, for hydroxyurea)[12] and Gao et al., Biochem Pharmacol 50:274 (1995) (substitution of 2'-F-dd-ara-A, another antiviral nucleoside phosphate analog, for ddI).[13] The claims cover use of a synergistic combination of an inhibitor of ribonucleotide reductase and an antiviral nucleoside phosphate analog other than a thymidine or cytidine analog. The phrases "an inhibitor of ribonucleotide reductase" and "an antiviral nucleoside phosphate analog" are as accurate as the subject matter permits, such components of a mixture being undefinable by "chicken wire" structural formulas known to organic chemists. As agreed by the MPEP, where, as here, a definition is by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, the written description requirement for a claimed genus is satisfied. The Patent Office maintained its rejection of the claims despite the Declaration of Dr. Vila. Factual evidence, however, must be accepted by the PTO. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996). The Patent Office's answer that the specification describes only

[11] Attachment 10 of record.
[12] Attachment 11 of record.
[13] Attachment 12 of record.

one working example, that of use of a combination of ddI and hydroxyurea, does not refute the thrust of the declaration which is that one with ordinary skill in the art would have understood the specification to describe use of a combination of the class of compounds to which ddI belongs in combination with the class of compounds to which hydroxyurea belongs. See, for example, original claim 10. Because of this understanding, the evidence weighs in favor of compliance with the written description requirement. Additionally, see Declaration of Dr. Lori,[14] a named inventor of the above-identified application, which provides post-filing date evidence of other representative combinations that work, as predicted by the patent specification, further supporting possession of the claimed genus.

As stated above, the definiteness issue is governed by MPEP § 2173.05(r). Due to the fact that no claim reads "A device substantially as shown and described," none of the claims is an omnibus claim. Consequently, the claims should not be rejected under 35 USC 112, second paragraph. The Patent Office maintained its rejection on the allegation that the claims by reliance on the terms "an inhibitor of ribonucleotide reductase" and "an antiviral nucleoside" are in effect omnibus claims. The MPEP, however, does not state that a claim which is "in effect" an omnibus claim should be rejected. It says that an omnibus claim should be rejected, where an omnibus claim reads as follows: "A device substantially as shown and described." Because the claims do not state the requisite language ("A device substantially as shown and described."), they are not omnibus claims and cannot be rejected under 35 USC 112, second paragraph. Additionally, the claims are as definite as the subject matter permits.

II. Discussion of Double Patenting

The Patent Office rejected the claims on the grounds of obviousness-type double patenting over claims 1-3 of USP 5,521,161, claims 1-3 of USP 5,736,527, claims 12-22 of USP 6,046,175, claims 6-8 of USP 6,093,702, and claims 3-8 of USP 6,194,390. Under MPEP 804 II B "Nonstatutory Double Patenting," obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent. A rejection based on a nonstatutory type of double patenting can be avoided by filing a terminal disclaimer in the application in which the rejection is made. The filing of a terminal disclaimer to obviate a rejection based on nonstatutory double

[14] Of record.

patenting is not an admission of the propriety of the rejection under Quad Environmental Technologies Corp. v. Union Sanitary District, 20 USPQ2d 1392 (Fed. Cir. 1991). The filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection. With respect to this rejection, Applicants respectfully submit that they will defer the filing of any terminal disclaimer until the rejected claim is otherwise indicated to be in condition for allowance.

III. Discussion of Patentability Of Claims As Not Being Anticipated

The Patent Office rejected the claims under 35 USC 102(b) as being anticipated by Palmer *et al.*, 1999 *Antimicrobial Agents and Chemotherapy* **43**:2046-2050. The claims must be patentable over the prior art; and the operative word is "prior." The effective filing date of this application is May 17, 1994, and the priority date is May 21, 1993. The reference date of Palmer et al. is Aug. 1999. Thus, the effective filing date of this application is prior to the reference date of Palmer et al 1999. Consequently, Palmer et al. 1999 does not qualify as *prior* art in terms of date.

In effect, by citing Palmer et al. 1999 as enabling prior art, the Patent Office agrees that the post-filing date art provides evidence of other representative combinations besides ddI and hydroxyrea that work, as predicted by the patent specification (for example, at page 6, lines 1-33), thus further supporting enablement and further supporting possession of the claimed genus. According to Declaration of Dr. Lori, 2 HU analogues, both inhibitors of ribonucleotide reductase, behave like HU: trimidox (Sumpter *et al.* 2004 *Antiviral Research* **62:**111-112) and didox (Sumpter *et al.* 2004 *Antiviral Research* **62:**111-112). Also according to Declaration of Dr. Lori, 2 antiviral nucleoside phosphate analogues (other than a thymidine or cytidine analogue) behave like ddI: abacavir, a guanosine analogue (Sumpter *et al.* 2004 *Antiviral Research* **62:**111-112) and PMEA, a adenosine analogue (Palmer *et al.*, 1999 *Antimicrobial Agents and Chemotherapy* **43**:2046-2050). In conclusion, not only are the claims patentable as not being anticipated, but also the claims meet the requirements of enablement and written description as discussed above and as supported by the Declaration of Dr. Lori and the requirement of definiteness as discussed above.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

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Dated: 12/17/04

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